Editorial

Hepatocellular carcinoma with macrovascular invasion: need a personalized medicine for this complicated event

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Hepatocellular carcinoma (HCC) is a hypervascular tumor and has a tendency to invade portal vein (PV) or hepatic vein (HV). HCC with macrovascular invasion (MVI) is associated with poor prognosis (1). HCC invasion of PV can lead to rapid intrahepatic tumor spread. In addition, portal vein tumor thrombus (PVTT) may result in deterioration of hepatic function, as well as increased risk of portal hypertensive complications (2). HCC invasion of HV is associated with increased risk of systemic metastasis. Furthermore, it can extend into the inferior vena cava and right atrium, causing sudden death as a result of massive pulmonary embolism or heart failure (3). Thus, surgical resection is typically not recommended, and standard first-line treatment for HCC with MVI is systemic therapy.

However, even with recommended systemic therapy such as sorafenib, HCC patients with MVI are still prone to rapid tumors progression (4). Although a better systemic treatment option (atezolizumab plus bevacizumab) has emerged (5), data of atezolizumab plus bevacizumab treatment focusing on HCC with MVI is still lacking. Therefore, considerable centers around the world still perform surgical resection for HCC with MVI when it is judged to be resectable in the belief of better prognosis. Indeed, several studies reported that surgical treatment showed the best outcomes in patients with HCC and PVTT in one or more segments (6,7). However, these studies were retrospective and non-randomized design, and selection bias cannot be avoidable; usually patients who received other locoregional therapy have inoperable diseases due to the extent of tumor, underlying poor liver functional reserve, or other combined morbidity. A well-designed randomized controlled trial would be required to prove superiority of surgical resection to other locoregional therapy; however, this would be difficult to conduct due to the current practice guidelines and ethical concerns.

Recently, Huang *et al.* (8) presented a meta-analysis reporting clinical outcomes of surgical resection for HCC with MVI including 40 studies involving 8,218 patients. This study may have a significant clinical impact because there has never been such a sizable study before. In this meta-analysis, the pooled median overall survival (OS) was 14 months [95% confidence interval (CI): 11–19 months], 1-year and 3-year OS were 54% and 23%, respectively. The pooled rate of major complications was 6% (95% CI: 4–11%). Most importantly, the median OS dramatically decreased with the increased extent of PVTT; median OS was 20 months in patients with segmental/2nd order PVTT, 13 months in patients with 1st order PVTT, and 6 months in patients with main PVTT. According to the results of the

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meta-analysis, they suggested that surgical resection may be a viable alternative option in the setting of segmental or 2nd order PVTT. Whereas, they suggested that invasive surgery should be avoided in HCC patients with 1st order or main PVTT, given the poor OS outcomes (8).

Despite the comprehensive literature search, this meta-analysis (8) is limited due to its analysis of retrospective observational studies (90%, 36/40) and lack of control arm. The majority of patients were from the Asia (93%, 7,611/8,218), especially from China (75%, 6,140/8,218). Therefore, clinical outcomes of surgical resection for HCC with MVI might be driven by that of China. In their meta-analysis (8), survival outcomes of surgical resection in China seemed to be significantly poor than other countries. Because of this, there would be a possibility that survival outcomes of surgical resection for HCC with MVI may be undervalued. Thus, more studies from western countries regarding this topic are urgently needed.

Although surgical resection showed promising outcomes (median OS: 20 months) in patients with segmental/2nd order PVTT in the meta-analysis (8), there were other potent locoregional therapeutic options for these specific indications (9-12). For instance, one retrospective study from Italy showed that median OS of HCC patients with segmental, 2nd order, and 1st order or main PVTT were 28, 12, and 8.2 months, respectively, after radioembolization in 120 HCC patients with PVTT (9). In a randomized controlled trial from South Korea (10), chemoembolization plus external beam radiotherapy showed better median OS than sorafenib treatment (14 *vs.* 11 months, P=0.04) in HCC patients with MVI. In addition, chemoembolization combined with systemic therapy (sorafenib or lenvatinib) showed promising outcomes in HCC patients with MVI (11,12). Above all, a sizable study regarding clinical outcomes of atezolizumab plus bevacizumab systemic treatment for HCC with MVI is eagerly waited.

HCC with MVI is a complicated event; prognosis differs significantly according to the tumor burden and extent of MVI, as well as underlying liver functional reserve or other comorbidities. As authors of the meta-analysis mentioned (8), a personalized approach should be adopted for HCC patients with MVI, instead of one-size-fits-all systemic therapy. For this, more sophiscated treatment guideline for HCC with MVI would be required; HCC with MVI should be subclassified by prognosis and best treatment option for each subclassified category should be searched from the future well-designed comparative studies.

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